claims as Exhibit 1. No new matter has been added by way of these amendments.

At the outset, applicants thank Examiner Crouch and Mr. Richard Schwartz for the helpful telephone discussion of the enablement rejection on March 31, 1997.

In the office action dated January 13, 1997, the examiner made two rejections. In response, applicants respectfully submit the following remarks.

I. Rejection of Claims Under 35 USC §112, First Paragraph

The examiner has rejected claims 2, 7, 12, 14, 17, 20, 21 and 24 under the first paragraph of 35 USC §112, on the basis that the specification does not enable the production of transgenic cows. Applicants respectfully traverse this basis for rejection.

At the outset, applicants note that the examiner has stated that Dr. Bondioli's Rule 132 Declaration fails to provide persuasive evidence for applicants' position that the present specification supports claims to transgenic cows. Yet Dr. Bondioli has stated that he has read and understood the present specification. See paragraph two of the declaration of Dr. Bondioli, filed December 17, 1996. He has also stated that the "major breakthrough" which enabled the production of transgenic cattle was the technique of centrifuging zygotes to allow visualization of pronuclei, and that this method was described in a 1987 publication referenced in the present application. See paragraph three of the Rule 132 declaration. Dr. Bondioli's review of the specification and his experience as an expert in producing transgenic cattle has led him to conclude that:

> [T]he scientific knowledge available as of January of 1991 in combination with the disclosure of the above-captioned application would have enabled a researcher to produce a transgenic cow having a transgene under the control of the "long WAP promoter."

Dr. Bondioli's Rule 132 Declaration at paragraph seven. Applicants submit that the examiner cannot simply disregard the conclusion of this *expert's* declaration.

The examiner has stated that:

> The production of transgenic cows, at least by a review of the art at the time of filing, appears to be problematic as at the time of filing there are no reports of the production of transgenic cows that produce recoverable amounts of protein routinely from their milk.

Office action at page two. Yet Dr. Bondioli stated in his declaration that "the observation that there are few reports of transgenic cattle by 1991 was strictly a function of economics, and was not due to a lack of technical know-how." Paragraph eight of the Rule 132 Declaration of Dr. Bondioli. Accordingly, the lack of publications on transgenic cows does not support a rejection based upon an alleged lack of enablement.

Nevertheless, applicants supplement Dr. Bondioli's expert opinion regarding the state of the art with the following observations.

- In 1991, Krimpenfort *et al., Bio/Technology 9*:844 (1991), described the production of a transgenic male calf that contained a human lactoferrin gene operatively linked to a casein promoter. [Exhibit 2]

- A review article by Lee *et al., J. Controlled Release 29*:213 (1994), states that the transgenic calf described in the Krimpenfort article was named "Herman." See page 217, column two, last paragraph and reference four of the Lee article. [Exhibit 3]

- An article published in the June 1, 1992, issue of *Biotechnology Newswatch* reported that the transgenic dairy bull, Herman, was ready to start producing a herd of cows that produce human lactoferrin in milk. [Exhibit 4]

- Dutton, *Genetic Engineering News 16*:37 (May 1, 1996), reported that Herman's transgenic offspring are producing human lactoferrin in their milk. See column three, fifth full paragraph, of the Dutton article. Moreover, the biological activity of human lactoferrin from transgenic cow's milk is indistinguishable from lactoferrin produced by humans. [Exhibit 5]

In sum, the methodology for producing foreign protein in the milk of transgenic cows was publicly available before the priority date of the present application. It is true that there is a gap between the time that those of skill in the art were capable of producing such transgenic cows and the actual production of transgenic cows that produce foreign protein in milk. However, this gap in time was not due to the requirement for undue experimentation. Instead, the lag was created merely because it requires a significant amount of time for cows to mature. In the above example, the first transgenic animal was male, and as result, time was required for the male to mature for breeding, and for the second generation of transgenic calves to be born and to mature for milk production. As Dr. Bondioli has attested, the observation that there are few reports of transgenic cattle by 1991 was not due to a lack of technical know-how.

Finally, the examiner has stated that:

> [E]ach of declarant's exhibits indicates that for transgenic cows, microinjected zygotes were fertilized in vitro for 7 days or to the morulae/blastocyst stage . . . . Either one of these conditions would indicate that in the production of transgenic cows, the implanted embryos was at 32-124 cell stage, whereas the specification teaches the direct implantation of microinjected zygotes into the mouse or pig. As all of the art provided teaches the in vitro maturation of cow or cattle microinjected zygotes, this appears to be necessary for the production of transgenic cows. Therefore, the exhibits supplied by declarant do not support the disclosure, but rather supply teaching not disclosed but appear necessary.

Office action at page 4.

Applicants respectfully reiterate Dr. Bondioli's statement that the technology for producing transgenic cattle was known before the priority date of the present application. In regard to the examiner's concern about the particular method of implantation, applicants refer to the 1991 Krimpenfort article. In the "Discussion" section, Krimpenfort *et al.* explain that there are two options for producing transgenic cattle. One can transfer microinjected zygotes directly into recipient cows (or into an intermediate host), or one can incubate microinjected zygotes to the morula/blastocyst stage *in vitro* before transferring the zygotes to a recipient cow. Although Krimpenfort *et al.* prefer the latter method, they note that the former method does have certain advantages. Thus, it is not true that production of transgenic cows *requires in vitro* maturation to the morula/blastocyst stage prior to implantation.

Significantly, ***both*** methods clearly were known to those of skill in the art by the priority date of the present application. Thus, it is not true that the technique of *in vitro* maturation became publicly available only after the priority date of the present application.

In light of the remarks above, applicants respectfully request the examiner to withdraw the rejection of the claims under the first paragraph of 35 USC §112. Reconsideration of the claims is respectfully requested.

II. Rejection of Claims Under 35 USC §112, Second Paragraph

The examiner has rejected claims 2, 4, 7, 9, 11 and 12 under the second paragraph of 35 USC §112, on the basis that the claims are indefinite. In particular, the examiner has stated that claims 2 and 7 are vague because the meaning of "portions of" is not clear. Applicants have amended the claims to make it clear that the DNA molecules include the following regulatory elements of the human protein C gene: the AUG start codon, donor and acceptor splice signals, the secretion peptide, translation

termination signal, transcription termination signal, and polyadenylation signal. Thus, this basis for rejection now is moot.

The examiner has rejected claims 4, 9 and 11, contending that the phrase "consisting essentially of" is proper only in a claim to a composition. Applicants note that the phrase describes DNA molecules, which are compositions. Nevertheless, applicants have amended the claims by substituting "comprising" for "consisting essentially of" to expedite prosecution. Thus, this basis for rejection now is moot.

The examiner has rejected claim 12 on the grounds that there is no antecedent basis for the terms "said protein" or "said peptide." Applicants believe that the examiner is referring to claim 14, not claim 12, in this rejection. Applicants have amended claim 14 to correct these informalities.

CONCLUSION

Applicants request reconsideration of the claims on their merits and respectfully solicit early notification of an allowance. If Examiner Crouch should have any questions or believes a telephone discussion would expedite prosecution, she is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

July 14, 1997
Date

Phillip B.C. Jones
Registration No. 38,195

FOLEY & LARDNER
P.O. Box 1497
150 East Gilman Street
Madison, Wisconsin 53701
Tel: (608) 258-4284